Medical Therapy for Benign Prostatic Hyperplasia: New Terminology, New Concepts, Better Choices

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This article discusses 3 areas of medical therapy for benign prostatic hyperplasia (BPH) that are undergoing extensive research and evaluation: 1) the use of muscarinic receptor antagonists to treat lower urinary tract symptoms (LUTS) in men with BPH; 2) the definition of an "enlarged prostate"; and 3) sexual function and LUTS. Fears of worsening obstructive symptoms or causing acute urinary retention often keep practitioners from prescribing muscarinic receptor antagonists to men who might have concomitant bladder outlet obstruction; a multicenter, multinational, double-blind study showed that tolterodine is safe for men with low postvoid residual volumes. Most urologists accept that a prostate volume of more than 40 mL is consistent with an enlarged prostate; there is more debate regarding prostate volumes of 30 to 40 mL. Recently presented data suggest that combination medical therapy might be effective for men having prostates with volumes of more than 25 mL. The association between voiding and sexual function has been increasingly recognized and investigated, and there seem to be common pathophysiologic mechanisms governing both conditions. Targeted treatment algorithms addressing both conditions seem warranted.
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Key words: Benign prostatic hyperplasia • Medical Therapy of Prostatic Symptoms trial • Overactive bladder • Bladder outlet obstruction • Detrusor overactivity • Muscarinic receptor antagonists

The paradigm for the medical management of benign prostatic hyperplasia (BPH) has been transformed over the past 15 years. This has been stimulated, in part, by new research, the approval of novel pharmaceutical and minimally invasive therapies, and the economics of health care financing. This transformation continues today. Indeed, as novel therapeutic modalities become available, as new connections between voiding symptoms and sexual function become identified, and as we learn which baseline parameters best predict

treatment response in specific patient populations, the therapeutic paradigm is likely to evolve, and progress, still further.

This article discusses 3 areas of medical therapy that are undergoing extensive research and evaluation: 1) the use of muscarinic receptor antagonists to treat lower urinary tract symptoms (LUTS) with predominant overactive bladder (OAB) symptoms in men with BPH; 2) the definition of "enlarged prostate," with a new look at the Medical Therapy of Prostatic Symptoms (MTOPS) trial; and 3) sexual function and LUTS.

Similar to LUTS, OAB symptoms are very common and increase in prevalence as men age. Whether or not LUTS and/or OAB symptoms are secondary to BPH and/or bladder outlet obstruction (BOO), the goal of treatment of symptoms should be to improve quality of life and to prevent clinical deterioration. A common dilemma when treating men with both BPH and OAB is the potential risk of acute urinary retention or worsening of postvoid residual urine volumes. The relationship of OAB to BOO, the role of urodynamics, and the use of muscarinic receptor antagonists is being increasingly scrutinized.

Prevalence and Significance of OAB in Men

Overactive bladder is a symptom complex specifically defined as "urgency, with or without urge incontinence, usually with frequency and nocturia . . . if there is no proven infection or other obvious pathology."[1] OAB symptoms are nearly identical to storage LUTS and affect an estimated 16% of men and 17% of women in the United States.[2] Milsom and colleagues[3] demonstrated that the prevalence of OAB symptoms increases with age, affecting an estimated 42% of men and 31% of women aged 75 years and older. OAB symptoms have adverse effects on quality of life, including increased depressive symptoms and diminished quality of sleep.[4] The National Overactive Bladder Evaluation program found the overall prevalence of OAB in men was 16% and also increased with age.[5]

The etiology of LUTS in men is manifold. Causes of LUTS include BPH, primary bladder neck dysfunction, urethral stricture, and neurourologic dysfunction. OAB symptoms are often caused by detrusor overactivity (DO), a urodynamic diagnosis characterized by involuntary contractions during the bladder filling phase.[6,7] Management of DO and resulting OAB symptoms can present particular challenges in men because of the significant comorbidity of BPH.

A survey of 5000 U.S. residents by the National Overactive Bladder Evaluation program found that the overall prevalence of OAB in men was 16% and increased with age.

BPH may cause BOO, which frequently coexists with DO or BOO may induce DO through ischemia and/or denervation of the detrusor muscle.[8-10] BOO is often characterized by and associated with increased detrusor collagen content.[11] These conditions can result in problems with emptying, filling/storage, or both—resulting in both irritative and obstructive voiding symptoms. In moderately or severely symptomatic men with LUTS, there is increased risk of urinary retention and/or symptom progression.[12]

The Role of Urodynamics in Evaluating OAB in Men

There is extensive urodynamic evidence that DO and BOO coexist. We reviewed the urodynamic records of over 2800 consecutive men over the age of 50 who were evaluated for LUTS. BOO was present in 62% of men. Of these, 66% had concomitant DO.[13] This is consistent with other series, which report concomitant BOO and DO in 40% to 60% of men.[14-17]

To understand the value of urodynamics in the longitudinal diagnosis and management of OAB, one has to appreciate the complex relationship between OAB symptoms and urodynamic measurements. It is common teaching that DO results in OAB symptoms. However, the direct link between OAB symptoms and urodynamic findings has been difficult to establish.[16,18] Symptom scores (eg, those assessed using International Prostate Symptom Scores [IPSS]) are not always predictors of urodynamic findings.[15,16,19]

The specific OAB symptoms of urge and urge incontinence have a stronger relationship to the urodynamic diagnosis of DO. In a study of 160 men with LUTS who underwent urodynamic evaluation, 68% had BOO and 46% had concomitant DO. Urge incontinence was correlated with the presence of DO.[16] In another study, the presence of DO correlated with perception of the urge symptom and quality of life on the IPSS.[19] Ultimately, the diagnostic value in assessing LUTS and, more specifically, OAB in men, remains to be determined.

The Effects of Muscarinic Receptor Antagonists in Men with DO and BOO

It is plausible that men who have OAB symptoms without concomitant urodynamic evidence of BOO would be less likely to benefit from therapies that target the prostate (eg, α-receptor antagonists and 5α-reductase inhibitors). Uroselective

α_1-adrenoreceptor antagonists (eg, tamsulosin and alfuzosin) are often chosen as initial therapies for symptomatic BPH. However, the low density of detrusor α-receptors may preclude direct effects of α-blockers on detrusor contractility, and α-blockers have demonstrated limited success in the treatment of OAB symptoms.[20,21] 5α-reductase inhibitors (eg, finasteride and dutasteride) inhibit the conversion of testosterone to the more potent androgen 5α-dihydrotestosterone (DHT) and are also used to treat BPH symptoms. However, endocrine changes mediated by 5α-reductase inhibitors are unlikely to alleviate DO and related OAB symptoms. Clearly, there is a need to further evaluate the efficacy and safety of pharmacotherapies to treat OAB in men with or without BOO, and to develop strategies for the appropriate use of these agents.

The rationale for use of muscarinic receptor antagonists to alleviate OAB symptoms has been well established. In part, this is based on the premise that detrusor contractility is regulated by the parasympathetic nervous system via muscarinic cholinergic pathways. Consequently, these agents are recognized as first-line therapy for OAB symptoms, with safety and efficacy well established.[22]

Given that muscarinic receptor antagonists improve OAB symptoms, why have they not been used in men to the same degree as in women? Traditional urologic teaching is that these agents should not be used in men who have OAB symptoms and BPH. This is due to concerns about decreasing bladder contractility and worsening obstructive symptoms and potentially causing acute urinary retention. However, more recent data suggests that these agents are safe in this group of men.

A multicenter, multinational, double-blind study examined safety concerns about using immediate-release tolterodine to treat men who had urodynamically diagnosed BOO and DO.[22] A total of 221 men were randomized to tolterodine 2 mg twice daily (n = 149) versus placebo (n = 72). They were followed for 3 months with urodynamics and for adverse events. Patients were excluded if they had a postvoid residual urine volume of 40% or more of maximum cystometric capacity or had prior prostate or bladder surgery. The majority of patients had moderate or severe BOO and were evenly distributed between tolterodine and placebo groups. There were no significant differences between the tolterodine and placebo groups with respect to the incidence of acute urinary retention (1 patient in each group) or in withdrawal from the study because of adverse events (6.0% with tolterodine and 6.9% with placebo). Changes from baseline in maximum flow rate (Q_{max}) and detrusor pressure at Q_{max} for tolterodine recipients were statistically equivalent to those with placebo. Of note, the median increase in postvoid residual volume was statistically significantly higher in the tolterodine group compared to placebo; however, this increase was clinically significant. An obvious question is what would happen to those patients with higher postvoid residual volumes at baseline who were excluded from the study? Are they at greater risk for urinary retention with anticholinergic medication?

Fears of worsening obstructive symptoms or causing acute urinary retention often keep practitioners from prescribing muscarinic receptor antagonists to men who might have concomitant BOO.

Another study examined the use of the combination of tolterodine and tamsulosin (an α-blocker) in men with BOO and concomitant DO.[23] A total of 50 consecutive Greek men with mild to moderate BOO and concomitant DO were evaluated. All patients were treated with tamsulosin 0.4 mg daily; 25 (50%) of the men were randomly chosen to also take tolterodine 2 mg twice daily. Quality-of-life (Urolife™) scores and urodynamic assessments were performed at baseline and after 3 months of therapy. Two patients (8%) in the tolterodine group withdrew from the study because of dry mouth symptoms, while 1 patient in each group withdrew because of orthostatic hypotension attributed to tamsulosin. Only patients on combination therapy (tamsulosin and tolterodine) had statistically significant improvements on quality-of-life scores. Men treated with a combination of an α-blocker and a muscarinic receptor antagonist experienced a significant reduction in maximum detrusor pressure during micturition, a significant increase in bladder capacity, lower maximum unstable contraction pressure, and higher volume at first unstable contraction. Both groups experienced a statistically significant increase in peak flow rate and volume at first unstable contraction. Most importantly, no patient experienced acute urinary retention during the study. Limitations of the study included lack of a placebo-controlled arm and short duration of therapy.

A more recent study was reported by Kaplan and associates.[24] In a prospective study, the researchers evaluated the safety and efficacy of tolterodine extended release in men with LUTS who had failed previous α-blocker therapy. In this study,

43 consecutive men, with LUTS secondary to BPH who had been treated with α-blocker therapy and had failed therapy were started on tolterodine extended release 4 mg once daily as monotherapy for 6 months. Of the 43 included patients, 39 (91%) completed the 6-month trial. The mean age of included patients was 61 years (range, 50–83 years), and the mean duration of previous α-blocker therapy was 5.7 months. α-Blockers included tamsulosin (n = 30), doxazosin (n = 9), and terazosin (n = 4), and α-blocker therapy failed because of adverse events (n = 11) and lack of efficacy (n = 32). Mean baseline PSA level was 2.3 ng/mL, and mean baseline International Index of Erectile Function (IIEF) erectile function domain score was 32.1 ± 9.8. Urinary frequency decreased from 9.8 to 6.3 micturitions per day ($P < .03$) and nocturia episodes decreased from 4.1 to 2.9 per night ($P < .01$). The changes in mean American Urological Association (AUA) symptom scores (−6.1, $P < .001$), Q_{max} (+1.9 mL/s, $P < .001$), and postvoid residual volumes (−22 mL, $P < .03$) after 6 months of treatment with tolterodine extended release were statistically significant. It is important to note that total AUA symptom scores were significantly reduced (−6.0, $P < .02$) after only 1 month of treatment. Mean scores for all individual OAB and voiding symptoms were also significantly reduced after 6 months of treatment with tolterodine extended release ($P < .02$).

Normal erectile function was noted in 27 men (63%) at baseline and in 29 men (67%) after 6 months of treatment. Mean total scores for the IIEF erectile function domain increased from 12.7 ± 4.3 at baseline to 19.6 ± 5.7 after 6 months of treatment with tolterodine extended release. There were no changes in ejaculatory function. Four men (9%) discontinued therapy with tolterodine extended release because of intolerable dry mouth. There were no occurrences of urinary retention.

This study was small in scale and did not employ a double-blind, placebo-controlled design. Furthermore, obstructive status was not urodynamically verified in participating patients. However, the results suggest that tolterodine extended release is an effective and well-tolerated treatment for LUTS secondary to BPH in the absence or presence of BOO. Furthermore, these data suggest that tolterodine extended release is effective in men who have not responded to treatment with α-blockers.

At this time, there are no published randomized-controlled trials describing the effects of other anticholinergic drugs or extended-release formulations of these drugs. Additionally, prospective studies of extended-release formulations in men with both DO and BOO would be ideal and informative.

As men age, the prevalence of both OAB and BOO secondary to BPH increase. Whether or not OAB symptoms are believed to be secondary to BOO, the treatment goal remains improving quality of life while preventing clinical deterioration.

What Is an Enlarged Prostate?

The idea of what constitutes an enlarged prostate is a moving target. Moreover, the best proxy for ascertaining that a prostate is enlarged is also in question. Is it volume or prostate-specific antigen level? Generally, most urologists accept that a prostate volume of more than 40 mL is consistent with an enlarged prostate. There is more debate regarding prostate volumes of 30 to 40 mL. Data presented at the 2005 meeting of the AUA suggest that combination medical therapy might be effective for men with prostate volumes of more than 25 mL.

The MTOPS Trial: A New Look

The MTOPS trial was the first study to assess the effect of medical therapy on the risk of overall clinical progression of BPH.[25] In this trial, the risk of clinical progression of BPH was significantly reduced by the α-adrenergic receptor blocker doxazosin (39% risk reduction) and by the 5α-reductase inhibitor finasteride (34% risk reduction), relative to placebo. Moreover, combination therapy with finasteride and doxazosin led to a significantly greater reduction in risk of overall clinical progression of BPH relative to placebo (66% risk reduction) compared with that for either drug alone.

The idea of what constitutes an enlarged prostate is a moving target.

Recently published guidelines from the AUA on the management of BPH incorporated the results of the MTOPS trial and recommended the combination of an α-blocker and a 5α-reductase inhibitor as an appropriate medical therapy option for men with LUTS associated with demonstrable prostatic enlargement.[26] However, when these guidelines were published, the relationship between baseline total prostate volume (TPV) and the effect of combination therapy versus either doxazosin or finasteride alone on the risk of clinical progression of BPH across the entire range of baseline TPV values had not been fully evaluated. Information on this relationship is necessary so that physicians can guide their decision making about when to recommend combination therapy to men with BPH. Kaplan

and associates[27] performed a secondary analysis of the relationship between baseline TPV and the effect of combination therapy with doxazosin and finasteride compared with either drug alone on the primary outcome of the trial, overall clinical progression of BPH, as well as on selected secondary outcomes.

Data from the MTOPS trial was examined to determine the relationship between baseline TPV and the effect of medical therapy in men with LUTS secondary to BPH. A total of 3047 LUTS patients were randomized to either placebo, doxazosin (4 to 8 mg), finasteride (5 mg), or the combination of doxazosin and finasteride. TPV was measured by transrectal ultrasound at baseline and at the end of the study.

All analyses were based on an intent-to-treat approach and included all patients with evaluable data. The investigators preplanned a secondary analysis of the relationship between baseline TPV and the effect of combination therapy versus doxazosin alone and combination therapy versus finasteride alone on the risk of the primary outcome of overall clinical progression of BPH, across clinically relevant, trichotomized, baseline TPV subgroups. The risk of overall clinical progression of BPH was determined with Cox proportional hazards regression analysis. On the basis of visual inspection of these data, 3 clinically relevant baseline TPV subgroups were chosen: less than 25 mL (small glands), 25 to 39 mL (moderately sized glands), and 40 mL or more (enlarged glands). In addition to the primary outcome of overall clinical progression of BPH, the researchers also examined the risk of invasive therapy for BPH as well as the mean between-group difference in the change from baseline at year 4 in AUA Symptom Score and Q_{max}, for combination therapy versus doxazosin alone and combination therapy versus finasteride alone, across these 3 baseline TPV subgroups.

The treatment groups were similar with regard to demographics and selected clinical characteristics at baseline (Table 1). Median baseline TPV for all patients was 31 mL (25th percentile: 23 mL; 75th percentile: 44 mL). Thirty-one percent of randomized patients had a baseline TPV of less than 25 mL, 38% had a baseline TPV of 25 to 39 mL, and 31% had a baseline TPV of 40 mL or more.

Overall Clinical Progression of BPH

In men with a baseline TPV less than 25 mL, there was no significant difference in the risk of BPH progression for combination therapy relative to doxazosin or finasteride alone (the relative risk [95% confidence interval (CI)] of BPH progression for combination therapy vs doxazosin alone and combination therapy vs finasteride alone in the subgroup with baseline TPV less than 25 mL was 0.74 [0.36-1.51] and 0.54 [0.27-1.09], respectively; Figure 1A). In the subgroups with TPV of 25 to 39 mL and 40 mL or more, the risk of overall clinical progression of BPH with combination therapy was significantly ($P < .05$) less than that with either doxazosin or finasteride alone (Figure 1A). The percentage risk reduction in overall clinical progression of BPH for combination therapy versus either doxazosin or finasteride alone was similar in the subgroups with baseline TPV of 25 to 39 mL and 40 mL or more, averaging approximately 50% in both subgroups (the relative risk [95% CI] of BPH progression for combination therapy vs doxazosin alone and combination therapy vs finasteride alone was 0.54 [0.30-0.96] and 0.55

Table 1
Baseline Characteristics in the MTOPS Trial

Characteristic	All Men (N = 3047)	Placebo (n = 737)	Doxazosin (n = 756)	Finasteride (n = 768)	Combination Therapy (n = 786)
Age (y)	62.6 ± 7.3	62.5 ± 7.5	62.7 ± 7.2	62.6 ± 7.3	62.7 ± 7.1
AUA Symptom Score	16.9 ± 5.9	16.8 ± 5.9	17.0 ± 5.8	17.6 ± 5.9	16.8 ± 5.8
Q_{max} (mL/s)	10.5 ± 2.6	10.5 ± 2.6	10.3 ± 2.5	10.5 ± 2.5	10.6 ± 2.5
Median TPV (mL)	31.0	30.6	31.1	31.0	31.4
PVR (mL)	68.1 ± 82.9	69.6 ± 82.1	69.2 ± 88.2	66.2 ± 80.0	67.5 ± 81.1
PSA (ng/mL)	2.4 ± 2.1	2.3 ± 2.0	2.4 ± 2.1	2.4 ± 2.1	2.3 ± 1.9

Data are presented as mean ± standard deviation, unless otherwise noted. MTOPS, Medical Therapy of Prostatic Symptoms; AUA, American Urological Association; Q_{max}, maximum urinary flow rate; TPV, total prostate volume; PVR, postvoid residual volume; PSA, prostate-specific antigen.

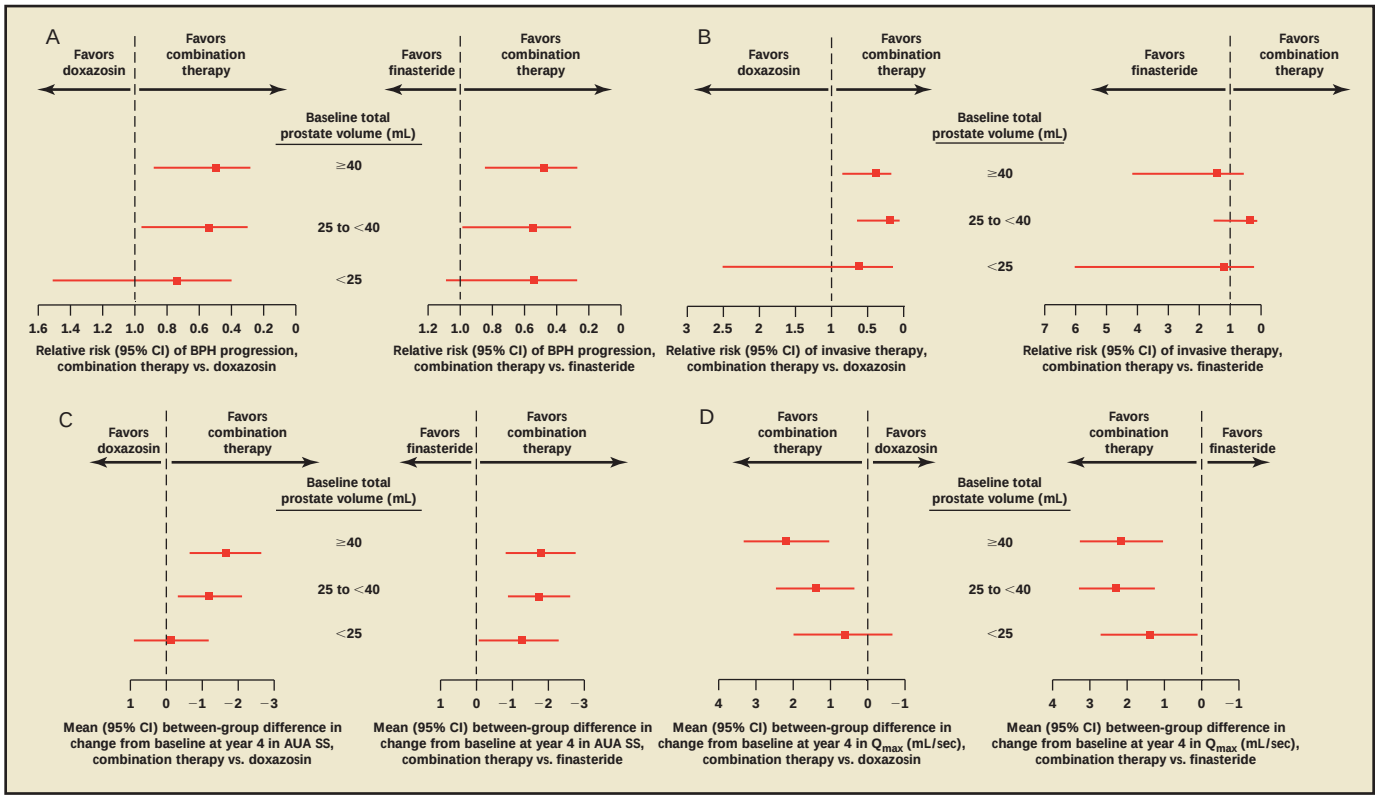

Figure 1. *Point estimates (with 95% confidence intervals [95% CI]) for comparison of effects of combination therapy versus doxazosin alone and combination therapy versus finasteride alone on* (A) *risk of overall clinical progression of benign prostatic hyperplasia (BPH);* (B) *risk of invasive therapy for BPH;* (C) *mean change from baseline in American Urological Association Symptom Score (AUA SS); and* (D) *mean change from baseline in peak urinary flow (Q_{max}), presented across the baseline total prostate volume subgroups of less than 25 mL, 25 to 39 mL, and 40 mL or more.*

[0.31-0.99], respectively, in the 25 to 39 mL baseline TPV subgroup, and 0.50 [0.28-0.88] and 0.48 [0.27-0.85], respectively, in the 40 mL or more baseline TPV subgroup).

Invasive Therapy for BPH

The relative risk of invasive therapy for men receiving combination therapy versus doxazosin alone and combination therapy versus finasteride alone was examined across the three baseline TPV subgroups (Figure 1B). For men with baseline TPV less than 25 mL, there was no significant difference in the risk of invasive therapy for combination therapy relative to doxazosin or finasteride alone. However, in the subgroups with baseline TPV of 25 to 39 mL and 40 mL or more, there was a significant ($P < .05$) and marked percentage risk reduction of invasive therapy of approximately 60% to 80% for combination therapy versus doxazosin alone (the relative risk [95% CI] of invasive therapy for combination therapy vs doxazosin alone was 0.19 [0.05-0.65] and 0.38 [0.17-0.85] in the 25 to 39 mL and 40 mL or more baseline TPV subgroups, respectively). There was no significant difference in the risk of invasive therapy for combination therapy versus finasteride alone in the subgroups with baseline TPV of 25 to 39 mL and 40 mL or more (the relative risk [95% CI] of invasive therapy for combination therapy vs finasteride alone was 0.38 [0.10-1.54] and 1.44 [0.50-4.16] in the 25 to 39 mL and 40 mL or more baseline TPV subgroups, respectively).

AUA Symptom Score

The mean between-group difference in change from baseline to follow-up at 4 years in AUA Symptom Score for combination therapy versus doxazosin alone and combination therapy versus finasteride alone was examined across the 3 baseline TPV subgroups (Figure 1C). In men with baseline TPV less than 25 mL, the improvement at year 4 in AUA Symptom Score for combination therapy versus doxazosin alone was not significantly different, whereas the improvement for combination therapy versus finasteride alone was significantly ($P < .05$) different in favor of combination therapy. In the subgroups with baseline TPV of 25 to 39 mL and 40 mL or more, the improvement in AUA Symptom Score with combination

therapy was significantly ($P < .05$) better than that for doxazosin alone and finasteride alone.

Maximum Urinary Flow Rate

For men with baseline TPV less than 25 mL, the improvement at year 4 in Q_{max} for combination therapy versus doxazosin alone was not significantly different, whereas the improvement for combination therapy versus finasteride alone was significantly ($P < .05$) different in favor of combination therapy (Figure 1D). In the subgroups with baseline TPV of 25 to 39 mL and 40 mL or more, the mean change from baseline in Q_{max} with combination therapy was significantly ($P < .05$) greater than that with doxazosin alone and finasteride alone.

One problem with this analysis was that as baseline TPV decreased below 25 mL, the BPH outcomes data became increasingly variable, making a reliable assessment of the relative effects of the active treatments on overall clinical progression of BPH difficult. Additional studies in LUTS patients with prostate volumes less than 25 mL are needed to determine definitively whether combination therapy results in a superior reduction in the risk of overall clinical progression of BPH versus either doxazosin or finasteride alone in these men.

In LUTS patients with small prostates (baseline TPV less than 25 mL), treatment with combination therapy led to a similar level of overall improvement as seen with doxazosin alone and a superior level of overall improvement relative to finasteride alone. In LUTS patients with moderately sized prostates (baseline TPV 25 to 39 mL) and those with enlarged glands (baseline TPV 40 mL or more), combination therapy led to a superior beneficial effect compared with either doxazosin or finasteride alone.

Relationship Between Sexual Function and LUTS

Epidemiology

The prevalence of BPH increases with age. In fact, advanced age and normal androgenic function are the 2 most well-established etiologic factors for the disease.[28] The presence of LUTS in men is suggestive of the presence of BPH.[29] Data from a general practice database in the United Kingdom indicate that the incidence of LUTS as a marker of clinically significant BPH increases linearly from the ages of 45 to 85 years, whereas the prevalence of BPH increases from 3.5% to 35% between the ages of 40 and 80 years.

The prevalence of BPH increases with age. In fact, advanced age and normal androgenic function are the 2 most well-established etiologic factors for the disease.

Symptoms of LUTS due to BPH can be divided into obstructive (static) and irritative (dynamic) components. Increased frequency of urination, nocturia, and urgency are all dynamic manifestations. These symptoms can be linked to an α_1-adrenoreceptor–dependent increase in smooth muscle tone, predominantly in the capsule of the prostate and bladder neck. In addition to the static and dynamic manifestations, the presence of BPH is associated with sexual dysfunction, independent of age and other comorbidities. Erectile dysfunction (ED), ejaculatory disturbances, and pain during sex are strongly correlated with the presence and severity of LUTS—manifestations that must be considered when selecting therapy for patients with BPH.

As noted above, recent research has focused attention on the nexus between LUTS and sexual function, particularly ejaculatory function. In questionnaires, patients have reported a high prevalence of bothersome symptoms, such as pain and discomfort during sex, retrograde ejaculation, impotence, and an inability to sustain an erection. These problems tend to worsen with age. In a recent study by Vallancien and colleagues,[30] sexual function of 1274 European men with LUTS was assessed using the Danish Prostate Symptom Score sexual function questionnaire. Erectile dysfunction, reduced ejaculation, and pain or discomfort on ejaculation were reported by 62%, 63%, and 23% of patients, respectively.[31] These findings have been further supported by both the Cologne Male Survey and the Multinational Survey of the Aging Male (MSAM-7).[31,32] In the Cologne Male Survey, 72.7% of men with BPH/LUTS had concomitant ED. LUTS was found to be an independent risk factor for the development of ED; ED was twice as high in men with LUTS. In MSAM-7, 49% of men aged 50 to 80 years from 6 countries had mild to complete ED; 77.6% rated it as bothersome. Furthermore, only 10% of men reported no symptoms of either BPH/LUTS or ED.

Pathophysiology

Norepinephrine, the endogenous ligand for adrenergic receptors, is the primary anti-erectile neurotransmitter. Both α- and β-adrenergic receptors are present in human corpus cavernosal tissue, the majority being α-receptors.[33] Studies of α_1-adrenergic–subtype expression in the smooth muscle of the corpora cavernosa indicate that both α_{1A}- and α_{1D}-receptors are the predominant subtypes and mediate contraction of the smooth muscle, maintaining a flaccid state.[34] In

addition, adrenergic activity suppresses the erectogenic response.

Relating to the physiology of ejaculation, the predominant adrenoreceptor subtypes in the bladder neck and vas deferens are α_{1A} and α_{1D}.[35] Inhibition of adrenoreceptor-mediated smooth muscle contraction at the bladder neck impairs creation of the pressure chamber necessary for normal ejaculation. Blockade of α_{1A}/α_{1D}-receptors has the potential to produce retrograde ejaculation—a class effect of α-adrenergic blockers.[36]

Although sexual activity normally diminishes with age, impaired sexual performance remains an undesirable side effect of BPH, and treatment often produces significant clinical improvement and symptom reduction.[37] Clinical evaluations have now confirmed previous studies in preclinical models showing that blockade of α-adrenergic activity can improve sexual function. As mentioned above, abnormal ejaculation is a class effect of treatment with α_1-adrenergic–receptor blockers, though it is rarely serious enough to prompt patients to withdraw from treatment (the risk of ejaculation disorders due to α-blocker therapy for BPH is much lower than that from surgical intervention for BPH). With some α-blockers, this phenomenon was thought to be due to higher affinity for α_{1D}-subtype receptors, but it has also been observed with "superselective" α_{1A}-subtype inhibitors.[38]

Other potential pathophysiologic mechanisms common to LUTS and ED have been reported. These include age-related atherosclerosis–induced vascular insufficiency in the bladder and corpora and autonomic nervous system hyperactivity potentially mediated by nitric oxide pathways.[39-41]

McVary and McKenna[42] have proposed that common etiologic factors, such as diabetes, smoking, and hyperinsulinemia, result in reduced nitric oxide synthase and nitric oxide levels. This leads to smooth muscle cell proliferation, increases in smooth muscle contractility, reduced compliance, and both LUTS and ED. Of interest, there are significant amounts of phosphodiesterase (PDE) types 4 and 5 in the transition zone of the prostate.[43]

Implications for Therapy

These data suggest that sympathetic activity might mediate both LUTS and ED. α-Blockers remain the staple of medical therapy for LUTS and are not associated with decreased libido or ED. Given a potential common etiology of LUTS and ED, a strategy that addresses both conditions is advantageous. Kaplan[44] has reported that both alfuzosin and tamsulosin improve both general and sexual quality of life in men with BPH and LUTS, and both can be used with those PDE inhibitors that are without specific contraindications. 5α-Reductase inhibitors have been increasingly used to treat men with enlarged prostate. These can be used safely in conjunction with PDE-5 inhibitors. Moreover, sildenafil as a sole agent was found to improve urinary scores in a small study.[45]

In conclusion, the association between voiding problems and sexual dysfunction has been increasingly recognized and investigated. There seem to be common pathophysiologic mechanisms governing both conditions. Targeted treatment algorithms

Main Points

- There is no doubt that detrusor overactivity (DO) and bladder outlet obstruction (BOO) coexist. In more than 2800 consecutive men older than 50 years who were evaluated for lower urinary tract symptoms (LUTS), 62% had urodynamic evidence of BOO; of these, 66% had concomitant DO.
- Although the urodynamic finding of increased DO is thought to result in symptoms of overactive bladder (OAB), the link between OAB symptoms and urodynamic findings has been difficult to establish; however, 2 independent studies suggest a relationship of the OAB symptoms of urge and urge incontinence with DO.
- A multicenter, multinational, double-blind study examining the incidence of urinary retention in men with DO and BOO treated with anticholinergics found that the use of tolterodine in men with low postvoid residual volumes (< 30 mL) is safe.
- Preliminary data from another study suggest that combination therapy with anticholinergics and an α-blocker is safe and effective at improving quality of life for patients with DO and mild to moderate BOO.
- A secondary analysis of data from the Medical Therapy of Prostatic Symptoms trial showed that, in LUTS patients with small prostates, treatment with combination therapy led to a similar level of overall improvement as seen with doxazosin alone and a superior level of overall improvement relative to finasteride alone. In LUTS patients with moderately sized and enlarged prostates, combination therapy led to a superior beneficial effect compared with either doxazosin or finasteride alone.
- The association between voiding problem and sexual dysfunction has been increasingly recognized and investigated; there seem to be common pathophysiologic mechanisms governing both conditions. Targeted treatment algorithms addressing both conditions seem warranted, and this association will be a fertile area of future research.

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